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Helicobacter pylori infection and gastrointestinal tract cancer biology: considering a double- edged sword reflection

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Dear Editor,

In their comprehensive review Mentis et al. [1] discussed some molecular biological mechanisms involved in *Helicobacter pylori* infection (*Hp*-I)-related gastric cancer (GC) biology such as the role of stem cells and the link between *Hp*-I and gastrointestinal microbiota (GI-M). Moreover, they posed some «unsolved conundrums» such as the following: *Hp*-I induces gastric and duodenal inflammation, but is only linked to GC. This claim, however, is incomplete, because *Hp-I* is also linked with duodenal adenomas/carcinomas [2]. Moreover, *Hp*-I induces lower GI tract inflammation, thereby promoting oncogenesis [3,4]. In this regard, we wish to add some additional data involving *Hp*-I in upper and lower GI tract oncogenesis.

Concerning the role of stem cells in *Hp*-I-related GC, we earlier reviewed [5] mechanisms of *Hp* and stem cell interaction in GC such as: activation of the Wnt/β-catenin signaling pathway; CagA impact on the fibroblast growth factor signal pathways implicated in the development of GC; enhancing transforming growth factor-β/bone morphogenetic proteins signal pathway involved in GC cells invasion; sonic hedgehog signaling dysregulation; and recruitment of mesenchymal stem cells and/or bone marrow-derived stem cells (BMDSCs), also mentioned in one original study (2004) by the authors [1], in the course of chronic inflammatory condition, that gains stepwise transformation to GC cells [5]. Likewise, such aforementioned mechanisms have been confirmed by more recent data [6], further indicated that *Hp*-I activates epithelial-mesenchymal transition pathway and induces the development of GC stem cells (CSCs), such as CD44(+) [7]. Regarding the latter aspect, by using CSC and/or BMDSCs marker CD44, the CD44(+) gastric CSCs appear to display the stem cell self-renewal properties. Moreover, *Hp* is responsible for CD44(+) increased expression, indicating a potential *Hp* induction of CD44(+) gastric CSCs implicated in gastric tumorigenesis [3]. Furthermore, our studies showed presence of cyclin D1 involved in GC cell proliferation, as well as CD34 expressed on hematopoietic stem cells and neovessels in human *Hp*-related GC specimens [8]. Beyond GC, our studies also showed CD44(+) augmented expression in human *Hp*-connected colorectal adenoma (CRA) and colorectal cancer (CRC) tissues [3]. Therefore, *Hp*-I could have an impact on colon oncogenesis by stimulating CSCs or recruiting BMDSCs, similar to upper GI *Hp*-I-connected chronic inflammation-metaplasia-dysplasia sequence and BMDSCs recruitment that contribute to oncogenesis [3]. Thus further large-scale relative studies are warranted.

BMDSCs might also contribute to the pathogenesis of Barrett's esophagus (BE) [9], a complication of gastroesophageal reflux disease (GERD), which predisposes to BE-related esophageal adenocarcinoma (EAC) development. In this concern, it has been proposed that chronic *Hp*-I induces atrophic gastritis accompanying by decreased acid secretion and acid reflux, thereby reducing the risk of GERD and its related BE and EAC. However, this conventional consideration might represent a

double- edged sword one view. Regarding the opposed view, the authors reported that *Hp*-I influences the GI-M composition including the presence of gastric species such as *Campylobacter* [1]. Hypochlorhydria induced by *Hp*-related atrophic gastritis, results in GI-M dysbiosis, which, beyond GC, could also contribute to BE-EAC sequence [10,11]. In this regard, *Campylobacter*, as main influential genera in *Hp*-connected atrophic gastritis specimens, and gastric atrophy-induced GM could contribute to gastric carcinogenesis [10]. Equally, data on BE biofilm show high atypical nitrate reducing *Campylobacter* species in BE which, via chronic inflammation, may contribute to the development of BE and/or its progression to EAC [11]. Therefore*, Hp*–induced *Campylobacte*r species and dysbiosis, through chronic esophageal inflammation may lead to EAC development [11,12] and thus further investigation is needed.

Concerning the role of molecular events involved in *Hp*-I-related GERD-BE-EAC sequence, we also summarized [13] *Hp* relative pathogenic mechanisms such as: *Hp* induction of GI tract oncogenic gastrin, which stimulates Barrett's EAC cells proliferation via Janus Kinase (JAK)2 and Akt-dependent nuclear factor-kappa B (NF-κB) activation, displays a anti-apoptotic effect through Bcl-2 protein and survivin upregulation, and induces the mitogenic cyclooxygenase (COX)-2 expression that contributes to GI tract carcinogenesis. Specifically, COX-2 derived prostaglandins (PGs) contribute to BE-associated cancer progression, by perpetuating chronic inflammation. Likewise, the PGs mitogenic and antiapoptotic properties are mediated through activation of certain aforementioned signaling pathways including NF-κB, Sarcoma family protein tyrosine (Src), JAK2/Signal transducers and activators of transcription (STAT)3, Extracellular-signal Regulated (ERK), mitogen-activated protein (MARK) and phosphoinositide-3-kinase–protein kinase B (PI3K/Akt) kinases. Moreover, *Hp*-I could provoke specific molecular changes (genetic instability, E-cadherin methylation, monoclonal antibody Das-1) linked with BE pathophysiology, and promotes Ki-67 expression predicting BE malignant progression. Finally, *Hp*-related metabolic syndrome disorders associated with GI-M dysbiosis also appear to be involved in GI tract carcinogenesis [13-15]. Therefore, *Hp* eradication might inhibit aforementioned oncogenic processes, and thus further studies are necessary.

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